Remarks

The Official Action dated May 4, 2001 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place this application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 1 and 30 are amended in accordance with the teaching of the specification on page 4, lines 21-24 and page 10, lines 14-17, and in response to the Examiner's comment at page 5 of the Official Action. A version with markings showing changes made is attached hereto. It is believed that these changes do not involve any introduction of new matter and do not raise any new issues, whereby entry is believed to be in order and is respectfully requested.

The Examiner's remarks in the Final Office Action are addressed below.

Claim Rejection – 35 U.S.C. § 103(a)

Claims 1-30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the Lowey et al U.S. Patent No. 3,870,790 in view of the Stupak et al U.S. Patent No. 5,162,117. The Examiner continues to rely on Lowey to teach a combination of pharmaceutical active and carrier of hydroxypropyl methyl cellulose or of hydroxypropyl methyl cellulose and ethylcellulose. The Examiner also asserts that Lowey teaches release of active over a prolonged period of time. Stupak is relied upon for teaching various excipients in the pharmaceutical art.

This rejection is again traversed and reconsideration is respectfully requested. The combination of the teachings of these two cited references does not suggest the presently claimed invention. Firstly, neither Lowey nor Stupak suggest the combination of polymers as recited in present claim 1. Therefore, the additional teachings of Stupak cannot then provide the invention as recited in the present claims. Furthermore, the combination of the teachings of these two references does not provide for the unobvious advantages of the extended

control release characteristic of the composition which is now positively recited in claims 1 and 30.

As the Examiner is well aware, for obviousness to be determined, the (1) claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) reasonable expectation of success is the standard with which obviousness is determined.

The Examiner states that since polymers such as hydroxypropyl methyl cellulose and hydroxyethylcellulose act so similarly, they are interchangeable in a pharmaceutical composition and thus it would have been obvious to one of ordinary skill in the art to use one or the other or a mixture of the two hydrophilic polymers. However, the Examiner fails to consider that it is the cited art that must suggest such interchangeability. Lowey teaches the use of hydroxypropyl methyl cellulose or the combination of hydroxypropyl methyl cellulose and ethylcellulose. Lowey does not suggest the use of ethylcellulose with hydroxyethylcellulose, or the use of ethylcellulose with hydroxyethylcellulose and hydroxypropyl methyl cellulose. For the present compositions to be rendered obvious, Lowey would have to suggest making the composition as recited in the present claims. Lowey does not teach or suggest such a claimed composition nor does Stupak. Lowey does not teach that his polymers act so similar that they can be interchanged with any other known polymer.

The Examiner's citing of *In re Kerkhoven* is not relevant to the present situation because the combination of the two compositions of Lowey and Stupak do not teach or suggest each and every limitation of the claimed invention (and thus a third composition, that claimed, is not obtained). This legal case is also not relevant because the presently claimed

invention is directed to an extended release composition where the active is extended for at least up to 20 hours. Lowey only teaches extended release of 1-8 hours (see abstract).

The Examiner points to the present specification where it is stated that for the second polymer HEC and/or HPMC can be used. This is no way suggests that the claimed invention is obvious. Furthermore, the prior art must teach or suggest all the claimed limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure, *In Re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed.Cir.1991).

The Applicants have surprisingly found that the presently claimed combination as recited for example in claim 1 provides for a sustained therapeutic effect for up to at least 20 hours with only a single dose and without any food effect. The presently claimed invention is also easy and inexpensive to manufacture and more efficient in providing a sustained release of pharmaceutical agents than any known controlled delivery systems. There has been a long felt need for a simple-to-make, cost-efficient extended release composition that could be used for a variety of different pharmaceutical actives and provide for a release effect of at least 20 hours. Neither Stupak nor Lowey's compositions provide for sustained release of an active ingredient for over 20 hours with a single dose. This is an unobvious advantage of the presently claimed compositions not realized by the prior art which dates back to 1972 in the case of Stupak.

Claim 30 further recites that the moisture content of the composition is less than 3%. Lowey teaches a carrier agent of a humidified HPMC together with EC, with a moisture content as high as 25%, and preferred moisture contents of from 20-25%. Such high levels of moisture content is deliberately introduced by the Lowey by spraying the carrier mixture with 35% ethanol/water mixture and also keeping the carrier agents overnight in a steam room or an oven chamber under conditions of high humidity (70% - 90%) because, according to the teaching of Lowey, it is important to attain moisture levels (20% - 25%) in the blend as this is

important to the ultimate performance of the tablet. Lowey teaches that by controlled variation of the moisture content of the HPMC-EC carrier powder, the duration of the release period (1-8 hours) of the active medicament may be controlled. The release of active medicament according to Lowey is also dependent on compression forces used during compression. Lowey emphatically concludes that "the release of active ingredient is, therefore controlled by the size and weight, moisture content and degree of compression pressure exercised on the lozenges, suppository or tablet at the time it is being formed from the pre-wetted powder and active medicament". Hydration or moisture content is important in Lowey's invention such that Lowey teaches the use of adjuvants that do not tend to dehydrate the product before or after tableting.

In contrast, the presently claimed composition incorporates the use of a combination of HPMC, HEC, EC and certain auxiliary ingredients with a moisture content of less that 3% with no pre-wetted carrier. Contrary to the Examiner's position that there exists no critically between 3% and 5% moisture content, this does represent a significant difference. The decreased moisture content helps to tablet the composition and further the extended release profile of the composition (up to at least 20 hours versus the prior art release of 1-8 hours). Compositions are highly desirable when they can be prepared simply and cost effectively and further when they can be taken less often by the consumer. Extended release formulations are more cost effective to take by the consumer and easier because fewer tablet dosages are required. Thus the presently claimed composition is highly desirable commercially.

Thus, the combination of the teachings of the references does not suggest to one skilled in the art that such specific elements of each reference may be combined to provide the presently claimed invention. Furthermore, there is no teaching in any of the cited references which would lead one of ordinary skill in the art to expect that any such combination of selected teachings would lead to a successful extended release formulation as

presently claimed. For these reasons, the presently rejected claims cannot be considered to be obvious in view of the combined teachings of the cited art.

It is believed that the above represents a complete response to the Examiner's rejection under 35 U.S.C. § 103(a) and places the present application in condition for allowance. Reconsideration and an allowance are requested.

Respectfully submitted,

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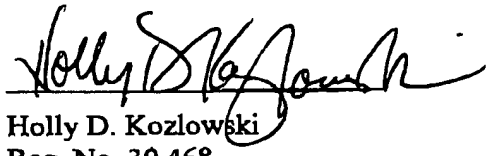

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CLAIM AMENDMENTS IN ACCORDANCE WITH 37 C.F.R. § 1.121(c)
SHOWING CHANGES MADE

1. (Twice Amended) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising hydroxyethylcellulose or a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight, [the polymer components being effective for controlled release of said pharmaceutically active substance from said composition]

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for up to at least 20 hours.

30. (Amended) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component comprising ethylcellulose

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising hydroxyethylcellulose, or hydroxypropyl methyl cellulose, or a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight, [the polymer

components being effective for controlled release of said pharmaceutically active substance from said composition] wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for up to at least 20 hours; and

wherein components (a), (b) and (c) are formulated as a homogeneous matrix and said composition has a moisture content of less than 3%.